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Comparative In Vitro Antibacterial Activities of Two New Oral Cephalosporins, Ceftetrame (Ro 19-5247) and Cefetamet (Ro 15-8074)

P. Y. CHAU,[1]* Y. K. LEUNG,[1] W. W. S. NG,[2] AND KEITH ARNOLD[3]

Departments of Microbiology[1] and Extra-Mural Studies,[2] University of Hong Kong, and Roche Far East Research Foundation,[3] Hong Kong

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The in vitro activities of two new oral cephalosporins, ceftetrame (Ro 19-5247) and cefetamet (Ro 15-8074), were tested against 990 clinical bacterial isolates in comparison with that of cephalexin. Both compounds were more active than cephalexin against gram-negative bacteria, inhibiting most isolates of the family *Enterobacteriaceae* at concentrations of ≤4 μg/ml, but were not active against *Acinetobacter* species, most *Pseudomonas* species, *Campylobacter jejuni*, and *Flavobacterium meningosepticum*. Ceftetrame was also more active than cephalexin against most streptococcal isolates and as active as cephalexin against methicillin-susceptible *Staphylococcus aureus*; against the latter cefetamet was ineffective.

Many newer cephalosporins with expanded spectra and increased antibacterial activities have been developed, but most of these can only be administered parenterally. Recently, two new oral cephalosporins of the pivaloyloxymethylester type, cefetamet (Ro 15-8074) and ceftetrame (Ro 19-5247), were developed (2, 4, 6–8). After absorption from the intestinal tract, the cephalosporin esters are rapidly hydrolyzed in the gut wall and in blood by esterase to release the active cephalosporins. Preliminary studies showed that a single oral dose of 400 mg of Ro 19-5248 (ceftetrame pivaloyloxymethylester) or 500 mg of Ro 15-8075 (cefetamet pivaloyloxymethylester) resulted in peak concentrations in serum of 3.8 μg of ceftetrame and 4.2 μg of cefetamet per ml, respectively (data on file at Hoffmann-La Roche & Co., Ltd., Basel, Switzerland). The achievable concentrations in serum of these two new oral cephalosporins are thus comparable to that of the other new oral cephalosporin, FR 17027, as levels of 4 μg/ml were achieved in serum after a 400-mg oral dose of FR 17027 (3). In this study, the in vitro activities of ceftetrame and cefetamet were tested against 183 gram-positive and 807 gram-negative bacterial isolates and compared with that of cephalexin.

Most bacterial strains tested in this study were isolated at the Clinical Microbiology Laboratory, Queen Mary Hospital, Hong Kong, over the past 2 years. Isolates of viridans group streptococci and *Acinetobacter anitratus* were from blood cultures. The production of β-lactamases in *Neisseria gonorrhoeae* and *Haemophilus influenzae* was confirmed by the chromogenic cephalosporin method (5).

MICs were determined by the agar dilution method with an inoculum size of 10^4 CFU per spot on the following antibiotic-containing media: Mueller-Hinton agar supplemented with 1% hemoglobin and 2% Vitox growth supplement (Oxoid Ltd., Basingstoke, England) for *N. gonorrhoeae*; heated blood agar for *H. influenzae*, *Listeria monocytogenes*, and *Neisseria meningitidis*; blood agar for *Streptococcus pneumoniae* and other streptococci; MacConkey agar (Oxoid) for *Proteus* species; and unsupplemented Mueller-Hinton agar (Oxoid) for all the other tested bacterial species. Ceftetrame and cefetamet (supplied as monosodium salts for in vitro testing) were obtained from Hoffmann-La Roche & Co., Ltd., and cephalexin was obtained from Eli Lilly & Co., Indianapolis, Ind. The MIC was defined as the lowest concentration of drug that inhibited visible growth after aerobic incubation at 37°C for 24 h, except for *Campylobacter jejuni*, which was incubated microaerobically with 5% O_2 and 10% CO_2.

The MIC ranges and MICs required to inhibit 50 and 90% of the tested isolates are shown in Table 1 (data for organisms with less than 10 tested strains, such as *N. meningitidis* and *Yersinia enterocolitica*, and for organisms resistant to the three tested cephalosporins are not listed in Table 1). Against *N. gonorrhoeae*, *N. meningitidis*, and *H. influenzae*, ceftetrame and cefetamet were 16 to 128 times more active than cephalexin, inhibiting all the tested isolates at concentrations of <0.25 μg/ml. Both compounds were also 8 to 64 times more active than cephalexin against isolates of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia rettgeri*, *Citrobacter freundii*, *Enterobacter aerogenes*, *Vibrio parahaemolyticus*, *Y. enterocolitica*, *Salmonella* species, and *Shigella* species, inhibiting all the tested isolates at concentrations of ≤4 μg/ml. Their activities did not appear to be affected by β-lactamases of the TEM type in *H. influenzae*, *N. gonorrhoeae*, *E. coli*, and *Salmonella typhimurium*, since both drugs were equally active against β-lactamase-producing and -nonproducing strains. The activities of ceftetrame and cefetamet were, however, relatively weak and inconsistent against strains of *Aeromonas hydrophila*, *Serratia marcescens*, *Enterobacter cloacae*, *Morganella morganii*, *Pseudomonas cepacia*, and *Pseudomonas pseudomallei*, with varied proportions of isolates of these bacterial species being resistant (requiring concentrations of ≥8 μg/ml for inhibition). Neither ceftetrame nor cefetamet was active against the following bacterial species (numbers of tested strains in parentheses): *A. anitratus* (128), *C. jejuni* (25), *Flavobacterium meningosepticum* (6), *Pseudomonas aeruginosa* (96), *Pseudomonas fluorescens* (11), *Pseudomonas maltophilia* (7), and *Pseudomonas putida* (7). It is of interest to note that although the activities of ceftetrame and cefetamet against gram-negative bacteria were generally comparable, ceftetrame was 8 to 16 times more active than cefetamet against *H. influenzae*, *M.*

* Corresponding author.

TABLE 1. Antibacterial activities of ceftetrame and cefetamet compared with that of cephalexin

Bacterial species (no. of strains)	Drug	MIC (μg/ml)[a]		
		Range	50%	90%
Gram-negative bacteria				
Aeromonas hydrophila (30)	Ceftetrame	0.06–16	0.5	2
	Cefetamet	0.015–16	0.5	2
	Cephalexin	8–>128	>128	>128
Citrobacter freundii (18)	Ceftetrame	0.125–1	0.25	0.5
	Cefetamet	0.015–0.25	0.06	0.125
	Cephalexin	4–>128	16	64
Enterobacter aerogenes (17)	Ceftetrame	0.25–4	0.5	2
	Cefetamet	0.06–2	0.25	1
	Cephalexin	32–>128	64	>128
Enterobacter cloacae (29)	Ceftetrame	0.125–64	0.5	64
	Cefetamet	0.015–>128	0.5	64
	Cephalexin	32–>128	64	>128
Escherichia coli, ampicillin susceptible (93)	Ceftetrame	0.03–2	0.25	0.5
	Cefetamet	0.03–4	0.25	1
	Cephalexin	2–16	4	8
Escherichia coli, ampicillin resistant (30)	Ceftetrame	0.03–4	0.25	2
	Cefetamet	0.03–2	0.25	2
	Cephalexin	4–16	8	16
Haemophilus influenzae, non-β-lactamase producing (18)	Ceftetrame	0.004–0.03	0.015	0.03
	Cefetamet	0.06–0.25	0.125	0.25
	Cephalexin	2–16	4	8
Haemophilus influenzae, β-lactamase producing (24)	Ceftetrame	0.008–0.03	0.015	0.03
	Cefetamet	0.06–0.25	0.125	0.25
	Cephalexin	2–16	4	8
Klebsiella pneumoniae (69)	Ceftetrame	0.03–1	0.25	0.25
	Cefetamet	0.03–2	0.125	0.25
	Cephalexin	2–128	4	8
Morganella morganii (16)	Ceftetrame	0.06–>128	0.5	8
	Cefetamet	0.5–>128	16	128
	Cephalexin	128–>128	>128	>128
Neisseria gonorrhoeae, non-β-lactamase producing (33)	Ceftetrame	0.001–0.125	0.015	0.06
	Cefetamet	0.0075–0.125	0.015	0.06
	Cephalexin	0.5–16	2	8
Neisseria gonorrhoeae, β-lactamase producing (31)	Ceftetrame	0.001–0.06	0.015	0.03
	Cefetamet	0.0075–0.06	0.015	0.03
	Cephalexin	2–16	2	16
Proteus mirabilis (76)	Ceftetrame	0.06–2	0.125	0.5
	Cefetamet	0.06–0.25	0.125	0.25
	Cephalexin	4–128	16	32
Proteus vulgaris (16)	Ceftetrame	0.06–4	0.25	4
	Cefetamet	0.03–1	0.25	1
	Cephalexin	128–>128	>128	>128
Providencia rettgeri (10)	Ceftetrame	0.03–0.5	0.125	0.25
	Cefetamet	0.015–0.25	0.06	0.125
	Cephalexin	>128	>128	>128
Pseudomonas cepacia (15)	Ceftetrame	8–>128	16	64
	Cefetamet	1–16	2	8
	Cephalexin	>128	>128	>128

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TABLE 1—*Continued*

Bacterial species (no. of strains)	Drug	MIC (μg/ml)[a]		
		Range	50%	90%
Pseudomonas pseudomallei (27)	Ceftetrame	8–16	8	16
	Cefetamet	2–4	2	4
	Cephalexin	>128	>128	>128
Salmonella typhi (17)	Ceftetrame	0.125–0.25	0.25	0.25
	Cefetamet	0.125–0.5	0.25	0.25
	Cephalexin	1–4	2	2
Salmonella typhimurium, ampicillin susceptible (15)	Ceftetrame	0.25–1	0.5	0.5
	Cefetamet	0.125–1	0.25	0.5
	Cephalexin	2–8	4	8
Salmonella typhimurium, ampicillin resistant (15)	Ceftetrame	0.125–4	0.5	2
	Cefetamet	0.25–1	0.5	1
	Cephalexin	4–16	8	16
Serratia marcescens (16)	Ceftetrame	1–8	1	8
	Cefetamet	0.5–4	0.5	4
	Cephalexin	32–>128	>128	>128
Shigella species (21)[b]	Ceftetrame	0.06–0.5	0.06	0.5
	Cefetamet	0.06–1	0.25	0.5
	Cephalexin	2–8	4	8
Vibrio parahaemolyticus (12)	Ceftetrame	0.06–0.25	0.06	0.06
	Cefetamet	2–8	4	4
	Cephalexin	8–64	32	64
Gram-positive bacteria				
Staphylococcus aureus, methicillin susceptible (44)	Ceftetrame	0.25–4	4	4
	Cefetamet	8–64	32	64
	Cephalexin	0.5–8	2	4
Streptococcus groups A, B, C, G, and R (29)[c]	Ceftetrame	0.004–0.06	0.004	0.03
	Cefetamet	0.015–1	0.03	1
	Cephalexin	0.06–2	0.125	0.5
Streptococcus pneumoniae (26)	Ceftetrame	0.004–0.015	0.015	0.015
	Cefetamet	0.06–0.25	0.25	0.25
	Cephalexin	1–2	1	2
Viridans group streptococci (31)	Ceftetrame	0.001–0.5	0.008	0.03
	Cefetamet	0.001–2	0.008	2
	Cephalexin	0.015–8	0.25	2

[a] 50% and 90%, MIC for 50 and 90% of the strains, respectively.
[b] Including 10 *Shigella flexneri* and 11 *Shigella sonnei* isolates.
[c] Including 8 *Streptococcus pyogenes* (group A), 5 *Streptococcus agalactiae* (group B), 4 *Streptococcus zooepidemicus* (group C), 5 *Streptococcus suis* (group R), and 7 Lancefield group G isolates.

morganii, and *V. parahaemolyticus*, while cefetamet was 4 to 8 times more active than ceftetrame against *P. cepacia* and *P. pseudomallei*; against these two *Pseudomonas* species ceftetrame was inactive. In fact, cefetamet and Augmentin (Beecham Laboratories; a combination of amoxicillin and clavulanic acid at a ratio of 2:1) are the only two oral β-lactam agents so far reported to have some potentially useful activity against *P. pseudomallei* (1).

Among the gram-positive isolates, all tested streptococci except *Streptococcus faecalis* were highly susceptible to ceftetrame, with all isolates being inhibited at concentrations of ≤0.5 μg/ml. Against these isolates the activity of ceftetrame was 4 to 16 times higher than those of cefetamet and cephalexin. The activity of ceftetrame against methicillin-susceptible *Staphylococcus aureus* was 8 to 16 times higher than that of cefetamet but comparable to that of cephalexin: the 44 tested isolates were inhibited by ceftetrame at concentrations of ≤4 μg/ml, while cefetamet concentrations of up to 64 μg/ml were required to inhibit these isolates. Neither ceftetrame nor cefetamet was active against methicillin-resistant *S. aureus* (23 strains tested), *S. faecalis* (25 strains tested), or *L. monocytogenes* (5 strains tested).

Data from this study indicated that the in vitro activity of cefetamet was similar to that of FR 17027, except that cefetamet was not active against *C. jejuni*, with MICs ranging from 32 to >128 μg/ml, while FR 17027 was reported to be active against this organism, with MICs ranging from

0.4 to 1.6 μg/ml (3). Neither FR 17027 nor cefetamet was active against *S. aureus*. The in vitro activity of ceftetrame was generally comparable to that of cefetamet against most gram-negative bacterial species but was significantly higher than that of cefetamet against *H. influenzae* and most gram-positive bacterial species. As the achievable levels of both ceftetrame and cefetamet in serum are well above the MICs for most of the bacterial isolates tested in this study, these two new oral cephalosporins may have a place in the initial treatment of upper and lower respiratory, genitourinary, and biliary tract infections and in the follow-up treatment of serious infections after a parenteral cephalosporin is given. Further evaluation of these two compounds is therefore justified.

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